The Pre-Submission Program and Meetings with FDA Staff

with LCDR Kimberly Piermatteo, MHA

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Hello, my name is Kimberly Piermatteo and I am a Consumer Safety Officer within the Center for Devices and Radiological Health at the Food and Drug Administration. The topic of this presentation is "The Pre-Submission Program and Meetings with FDA Staff."

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The following four learning objectives will be addressed during this presentation. The first learning objective is to understand what a Q-Submission is, how to submit a feedback request to the FDA and important reminders when making such a request.

Next, you will gain a better understanding of the various types of requests for FDA feedback that are tracked as Q-Submissions. Third, I will provide you with an overview of the recommended information which should be submitted in these requests for feedback. And lastly, I hope to give you a better understanding of when certain feedback requests are appropriate and when they are not.

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We will accomplish these learning objectives by covering each of the following topics outlined on this slide. We will first review Q-Submissions in general, then we will discuss each of the following individually; Pre-Submissions, Informational Meeting requests, Study Risk Determination requests, Formal Early Collaboration Meetings, Submission Issue Meeting requests, and we will wrap up with Day 100 Meetings for Premarket Approval or PMA Applications.

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To begin, let us discuss Q-Submissions generally.

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In order to understand Q-Submissions it is important to provide some background information. FDA made a commitment to industry and Congress to establish and maintain a structured process for managing requests for feedback prior to a premarket submission. Therefore, on February 18, 2014, the guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff" was finalized. This guidance provides information regarding existing mechanisms for requesting FDA feedback as well as also establishes several new mechanisms for feedback.

Information provided in the guidance includes logistics for submissions, tracking and review of responses to requests for both the Center for Devices and Radiological Health, or CDRH, as well as the Center for Biologics Evaluation and Research, or CBER.

Although this guidance provides advice for products reviewed by both CDRH and CBER, this presentation will provide information from a CDRH perspective only.
I recommend you thoroughly review this guidance, which is accessible via the link provided on this slide.

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The focus of this presentation will be to discuss the feedback mechanisms specifically outlined in the guidance. These are: Pre-Submissions or Pre-Subs; Informational Meeting requests; Study Risk Determination requests; Formal Early Collaboration Meetings; Submission Issue Meeting requests; and Day 100 Meetings for PMA Applications.

FDA has established one organizational structure to track the feedback mechanisms addressed in this guidance which are referred to as Q-Submissions or Q-Subs.

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Per the guidance, the feedback requests listed on the previous slide fall within the same Q-Sub organizational structure for tracking purposes. These types of requests for feedback will be assigned a unique identification number starting with the letter "Q" followed by the two digit year, and four digits representing the order in which the request was received during that calendar year. For example, the first Q-Sub received in January 2015 would have been identified as Q150001.

Supplements and Amendments to Q-Subs will be tracked similarly and will be identified in sequential order as S001 for supplement 1 or A001 for amendment 1.

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When submitting a Q-Sub, three copies are required. One of those three copies must be an electronic copy or eCopy. For more information on eCopies, sponsors should refer to the guidance on the "eCopy Program for Medical Device Submissions." A reference to this guidance is provided at the end of this presentation.

Like other submissions to the FDA, Q-Subs must be submitted through the Document Control Center or DCC at the address provided on this slide.

Once the FDA receives a Q-Sub request, the eCopy will be validated and then the FDA will send an acknowledgement letter containing the unique Q number to the sponsor.

For a subset of Q-Subs including Pre-Submissions, Informational Meeting requests and Submission Issue Meeting requests, FDA will conduct an acceptance review within 14 calendar days of receipt of the Q-Sub. This is to ensure there is sufficient information for FDA to provide the requested feedback for these types of Q-Subs.
If FDA determines that the information provided is insufficient, the request will be refused to accept or RTA and the sponsor should provide the additional information which will be logged in as an amendment to the Q-Sub.

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When submitting a Q-Sub, sponsors should remember the following:

Sponsors should clearly identify the desired mechanism for feedback and submissions should be in English.

Information provided in a request should be clear and concise.

An eCopy must be provided. The request will not be accepted if one is not provided.

Lastly, sponsors are reminded that feedback requests are subject to disclosure per the Freedom of Information Act also known as FOIA.

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Most of the mechanisms for feedback addressed in the guidance are for specific types of meeting requests; however, for a Pre-Submission sponsors can request a meeting as their preferred method for feedback. Study Risk Determination requests do not have the option for a meeting request.

There are a few important things to remember when a sponsor requests a meeting with the FDA.

Foremost, there are a variety of factors which may affect the scheduling of a meeting request. Factors include suggested dates and times, the availability of FDA staff, the completeness of the background information provided and the complexity of the issues can all affect the scheduling of a meeting request.

Secondly, FDA encourages sponsors to consider requesting a teleconference instead of an in-person meeting whenever possible and appropriate.

Thirdly, in order to ensure that FDA staff have time to review and prepare for a meeting request, sponsors should provide complete background information that is targeted and focused at the time of their initial request. If new or modified background information is provided after the initial request, the meeting may have to be rescheduled.

Additionally, FDA recommends meetings no more than one hour long. If a sponsor believes they need more time than one hour for a meeting they should provide their rationale for the duration they propose in their request.

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It is also important to note for an in-person meeting at an FDA facility, foreign visitors require advanced security clearance. Please refer to the guidance for details on how to request security clearance for foreign nationals.

If a presentation is planned for the meeting, these slides should be provided electronically to the FDA at least two business days prior to the meeting. Presentation slides should contain the same content as provided in the background information.

On the day of a meeting, sponsors should arrive at least 30 minutes before the scheduled meeting to undergo security screening and set up. During the meeting, attendees are not permitted to record the meeting by audio or video means.

Lastly, after a meeting, sponsors should submit draft minutes as an amendment to the Q-Sub through the Document Control Center within 15 calendar days of the meeting.

These are just a few reminders when requesting a meeting with the FDA. Sponsors should refer to Section Four of the guidance for specific details regarding meeting requests as well as to the sections within the guidance for the specific Q-Sub type.

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Next we will discuss Pre-Submissions or Pre-Subs.

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I'd like to begin by providing you some background information. Requests for feedback prior to a premarket device submission began with the establishment of the pre-investigational device exemption or pre-IDE Program in 1995. The pre-IDE program was originally designed to provide applicants with a mechanism to obtain FDA feedback on future IDE applications, prior to their submission.

The pre-IDE program evolved overtime to include requests for feedback on PMA applications, Humanitarian device exemptions or HDE applications, de novo petitions, and premarket notification or 510(k) submissions. This program became the most commonly used mechanism for requesting FDA's feedback prior to a premarket device submission. Thus the FDA changed the name for this program from the pre-IDE program to the Pre-Submission or Pre-Sub program.

The Medical Device User Fee Amendments of 2012, also referred to as MDUFA III, established a structured process for managing Pre-Submissions providing additional transparency to the IDE and premarket review processes.

Pre-Subs are defined as a formal written request for feedback from the FDA to help guide product development and/or application preparation. Pre-Subs may be submitted for an IDE Application; for a Non-significant risk or NSR device, for an Exempt Diagnostic device, for studies conducted outside the United States which are also referred to as OUS Studies; for a 510(k); for a de novo request; for a PMA; for an HDE; or for an In Vitro Diagnostic. Pre-Subs are not a required submission and are entirely voluntary on the part of the sponsor.

However, Pre-Subs are strongly encouraged in situations when specific questions arise which are not adequately addressed by existing guidance documents. Sponsors can request feedback from the FDA in a Pre-Sub in variety of ways such as through an in-person meeting, teleconference, fax or email. Sponsors may choose whichever way that best suits their specific situation. FDA will aim to provide complete feedback to a Pre-Sub request within 75 days, but no later than 90 days after receipt of a complete package. In rare cases where there is an urgent public health issue, FDA will aim to schedule a Pre-Sub meeting request within 21 days or sooner, if possible.

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FDA recommends that a Pre-Sub include the following information in a clear and concise format.

A cover letter should be included, which states the reason for the submission, such as if it is a Pre-Sub for a 510(k) or a Pre-Sub for an IDE. Contact information including the company name, address, contact person, phone number, fax number and email address, as well as the name of the device and the signature of the Pre-Sub contact person or responsible party should also be provided.

The CDRH Premarket Review Submission Cover Sheet, or Form FDA 3514, should be provided and sponsors should clearly indicate under Section A that the submission type is a Pre-Sub under Request for Feedback. To facilitate the review sponsors should provide a table of contents at the beginning of their Pre-Sub referencing content and relevant page numbers. A detailed device description should also be provided. Details may include pictures of the device, engineering drawings, list of materials, etc. A Pre-Sub should also include the proposed intended use of the device. Intended use should include the disease or condition that the device is indicated to prevent, mitigate, screen, monitor, treat or diagnose; the target population; the frequency of use; and whether the device is prescription use or over the counter use.

For in-vitro diagnostic devices, this should also include a detailed draft of the intended use of the device including the intended use population, the analyte or condition to detect and the assay methodology. Sponsors should also include a summary of previous discussions with the FDA regarding this device, including the submission numbers as well as an overview of the product development, including an outline of nonclinical and clinical testing either planned or already completed.

Importantly, a Pre-Sub should include specific questions regarding review issues relevant to a planned IDE or marketing application. This is important because FDA advice will be guided by the questions asked.

Lastly, sponsors should also clearly identify their preferred method of feedback in their Pre-Sub, such as via email, in-person meeting, teleconference or fax.

For a detailed checklist of the information that should be included in a Pre-Sub, please refer to the Pre-Sub Checklist in Appendix 2 of the guidance.

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Questions submitted in a Pre-Sub request should be targeted and focused. Sponsors should thoroughly review Appendix 1 of the guidance for specific examples of when a Pre-Sub is appropriate for specific submission types.

Some examples of when a Pre-Sub is appropriate are: Is our proposed trial design and selected control group appropriate? Another example of an appropriate question would be, does the FDA concur with the use of the proposed alternative test method, which is different than the normally recognized standard? Other examples include: Is a "moderate level of concern" the appropriate level of concern for my software? What specific information about a post-approval study should the PMA contain? Are the proposed study designs for demonstrating precision and accuracy adequate to support use of the assay in the Phase 3 clinical study? These are all appropriate Pre-Sub questions.

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A Pre-Sub is not is appropriate for all situations or requests for information from the FDA. Sponsors should review Section III.A.3 of the guidance for specific examples of when a Pre-Sub is not appropriate.

Some of those situations when a Pre-Sub is not appropriate include: requests for general information or questions regarding FDA policies and/or procedures; and requests for FDA to design a device's study protocol or clinical trial. Additionally, a Pre-Sub should not be a replacement for a sponsor to conduct their own research and analysis of current device practices applicable to their device.
A Pre-Sub is also not appropriate for questions that could be readily answered by reviewers and do not require the involvement of the FDA supervisor or more experienced staff. A Pre-Sub is also not part of the interactive review process for 510(k)s, IDEs, PMAs, or HDEs. For more information on interactive review processes please refer to the guidance "Types of Communication During the Review of Medical Device Submissions." A reference link to this guidance is provided at the end of this presentation.

Lastly, a Pre-Sub is not appropriate to appeal a decision on a premarket application. Nor is a Pre-Sub appropriate for requesting jurisdictional designation or device classification.
There are other mechanisms addressed in the guidance which we will discuss later in this presentation that are also not appropriate for Pre-Subs.

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A few reminders about Pre-Subs…The Pre-Sub program is not meant to be iterative. The FDA intends to provide one-time advice on topics associated with a Pre-Sub request. However, if sponsors expect to submit more than one Pre-Sub for additional topics for the same device, FDA recommends that the initial Pre-Sub request contain an overview of the expected submissions including general timeframes, if known.

Another reminder is that FDA review of a Pre-Sub does not guarantee approval or clearance of a future marketing application. Additionally, per the MDUFA III Commitment Letter dated April 2012, FDA intends to stand behind their feedback provided in a Pre-Sub request unless the circumstances significantly change, such as changing the intended use after FDA has already provided their feedback.

Lastly, sponsors should reference previous communications with FDA, such as a feedback received from FDA through a Pre-Sub in future relevant submissions.

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The next type of Q-Sub we will cover is Informational Meeting requests.

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Informational meetings are appropriate when an applicant or sponsor wants to share information with FDA without the expectation of feedback.
FDA will be in listening mode. If a sponsor wants FDA feedback on information they provide they should consider submitting a Pre-Sub.

FDA will aim to schedule an Informational Meeting or Teleconference within 90 days of receiving the meeting request as resources permit.

An Informational Meeting may be appropriate when a sponsor wants to provide an overview of ongoing device development when there are multiple submissions planned within the next year or so, or when a sponsor wants to familiarize the FDA review team about a new device that has significant technological differences from current devices.

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The following information should be included in an Informational Meeting Request. A cover letter should be included which clearly states the Q-Sub type is an Informational Meeting request. The CDRH Premarket Review Submission Cover Sheet, or Form FDA 3514, should also be provided and sponsors should clearly identify the type of request for feedback as an Informational Meeting.
Sponsors should also provide a brief statement about the meeting including the purpose, scope and/or objectives which the sponsor wishes to achieve.
Sponsors should also provide a proposed agenda which includes details about the device and/or topics to be discussed during the meeting. The preferred meeting format, such as in-person or teleconference, as well as preferred dates and times should also be included in the request.

FDA recommends that sponsors submit three or more preferred dates. Sponsors should also provide FDA with a list of the planned meeting attendees. And lastly, sponsors should indicate whether or not any audiovisual equipment is needed for the meeting. For a detailed checklist of the information that should be included in an Informational Meeting Request, please refer to the Informational Meeting Request Checklist in Appendix 2 of the guidance.

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Next, let us discuss Study Risk Determination requests which are also being tracked as Q-Subs.

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Sponsors of not exempt clinical studies are responsible for making the initial risk determination, but FDA is available to assist sponsors, clinical investigators or Institutional Review Boards, which are also referred to as IRBs, in making such a risk determination.

FDA will review the study protocol and issue a letter to the sponsor indicating whether the study is exempt or if not exempt whether the study is a significant risk or non-significant risk. This letter may be submitted to IRBs who then do not need to conduct their own independent assessment of the study risk because FDA's determination is final. It is important to remind sponsors that a study risk determination request does not obligate the sponsor to submit a future IDE application.

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The following information should be provided in a request for a Study Risk Determination. Sponsors should clearly indicate that the submission is a Study Risk Determination in their cover letter as well as on the CDRH Premarket Review Submission Cover Sheet, or Form FDA 3514. Sponsors should also provide a detailed device description, the study protocol, the target population, as well as their contact information.

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For additional information regarding Study Risk Determination requests please refer to the Q-Sub Checklist in Appendix 2 of the guidance as well as the guidance "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignificant Risk Medical Device Studies" available via the link provided on this slide.

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An existing mechanism of feedback that is now tracked as a Q-Sub is Formal Early Collaboration Meetings.

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Formal Early Collaboration Meetings were established in 1997 as a result of amendments to the Food, Drug and Cosmetic Act by the FDA Modernization Act. There are two types of early collaboration meetings - Determination meetings as described in section 513(a)(3)(D) of the FD&C Act, and Agreement meetings as described in section 520(g)(7) of the FD&C Act. Determination and Agreement meetings are tracked under the same Q-Sub organizational structure as the other feedback mechanisms discussed in this presentation; however, they are for specific purposes as described in the FD&C Act.

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For specific information regarding when early collaboration meetings are appropriate as well as the recommended content of a meeting request, please refer to the FDA guidance "Early Collaboration Meetings Under the FDA Modernization Act" available via the link provided on this slide.

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Next we will discuss Submission Issue Meeting requests.

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A sponsor may request a Submission Issue Meeting to discuss deficiencies identified during the premarket review of a 510(k), de novo, IDE, PMA, or CLIA waiver by application. The purpose of the meeting is to clarify FDA's questions and/or discuss the sponsor's approach to responding to complex issues.

FDA will aim to schedule Submission Issue Meeting requests within 21 days of the receipt of the meeting request.

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The following information should be provided in a request for a Submission Issue Meeting. Sponsors should clearly indicate that the submission is a Submission Issue Meeting request in their cover letter as well as in the CDRH Premarket Review Submission Cover Sheet or Form FDA 3514. Sponsors should reference the premarket submission number and any other related documents. A brief statement including the purpose, scope or objectives of the meeting should be provided as well. A proposed agenda should be included which clearly describes the deficiencies for discussion and the estimated time for each agenda item. Additionally, requests should include focused questions for which the sponsor is seeking guidance from FDA, if applicable. Sponsors should also provide the preferred meeting format, preferred dates and times, as well as the planned attendees and the identification of any audiovisual needs.
For a detailed checklist of the information that should be included in a Submission Issue Meeting request, please refer to the Submission Issue Meeting Request Checklist in Appendix 2 of the guidance.

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Submission Issue Meetings are not always appropriate when a sponsor has questions regarding a premarket submission. A Submission Issue Meeting request is not appropriate for brief clarification questions that do not require management participation and which can be readily addressed by the lead reviewer. It is also not appropriate if the sponsor desires FDA feedback on a proposed protocol prior to conducting a major study to address a deficiency. This type of feedback should be requested through a Pre-Sub. FDA will not pre-review sponsor's planned responses in a Submission Issue Meeting. As with a Pre-Sub, a Submission Issue Meeting is not appropriate for interactive review.

As stated earlier, for more information about interactive review processes, please refer to the guidance "Types of Communication During the Review of Medical Device Submissions - Guidance for Industry and Food and Drug Administration Staff."

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The last Q-Sub we will discuss is the Day 100 Meetings for Premarket Approval or PMA Applications.

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Day 100 meeting requests are for original PMAs and Panel-track PMA Supplements, and are a subset of Submission Issue Meetings. A PMA applicant may request a Day 100 Meeting. As outlined in the FDA Modernization Act also known as FDAMA, FDA will meet with an applicant no later than 100 days after receipt of a PMA application.

Prior to the meeting, FDA will inform the applicant in writing of any identified deficiencies based on an interim review of the entire application and what information is required to correct those deficiencies. FDA recommends that applicants request a Day 100 Meeting in their original PMA application or as a Q-Sub no later than 70 days from the PMA filing date so that FDA has sufficient time to schedule the meeting.

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A Day 100 Meeting Request should include the preferred meeting format such as in-person meeting or teleconference, as well as a list of planned attendees and preferred meeting dates and times. Applicants may choose to submit additional background information or other meeting materials prior to the Day 100 Meeting, but such information is not required.
For additional information on Day 100 Meetings, please refer to FDA's: "Guidance on PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies - for Use by CDRH and Industry" available via the link on this slide.

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A few reminders regarding Day 100 Meeting requests is that these are pre-defined meetings. These requests should be submitted with the original PMA, but can be submitted as a Q-Sub no later than 70 days from the PMA filing date. FDA and the applicant may, by mutual consent, establish a different time for the Day 100 Meeting. And lastly, FDA will communicate the identified deficiencies to the applicant within 90 days from the filing date of the PMA or 10 days prior to any Day 100 Meeting.

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In summary, Q-Submissions or Q-Subs are used to track various mechanisms for requesting feedback from the FDA. We discussed six types of feedback requests that are tracked as Q-Subs. First, we discussed Pre-Submissions or Pre-Subs, which provide sponsors with an opportunity to obtain FDA feedback prior to an intended premarket submission. Then we discussed Informational Meeting requests for when a sponsor wants to share information with FDA without the expectation of feedback. We also discussed Study Risk Determination requests to help a sponsor, investigator, or

IRB in making the risk determination of a clinical study. Then we discussed Formal Early Collaboration Meeting requests, which are defined by the statute as determination or agreement meetings. Next, we covered Submission Issue Meetings, which can be requested to discuss deficiencies identified during a premarket review. And lastly, we discussed Day 100 Meetings for PMA Applications which may be requested to discuss the review status of a PMA application. All of these requests are tracked as Q-Subs.

We also discussed the specific information that is recommended for each type of Q-Sub request. And finally, we discussed some examples of the types of questions and/or situations which are appropriate for each specific Q-Sub type.

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The following two slides provide references to the documents and forms cited earlier in the presentation.

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Please refer to these resources for additional information regarding each of these topics.

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Lastly, we encourage you to utilize the industry education resources listed on this slide. These resources are designed to help you further understand and comply with medical device regulations and policies. Thank you.

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